INTRODUCTION

The sigma-1 receptor (S1R) is a chaperone protein of the mitochondrion-associated endoplasmic reticulum membrane (MAM). Its expression is dysregulated in various cancers including glioblastoma, and ligand binding may decrease the proliferation of human glioblastoma cell lines. Thus, S1R characterization in glioblastoma could help to better understand the pathophysiology of this cancer and to improve diagnosis or treatment follow-up.

OBJECTIVES

We aim to evaluate the potential of (S)-(−)-[18F]fluspidine, a highly specific S1R radioligand already applied in clinical studies, to characterize S1R expression in an orthotopic glioblastoma model in mouse with small-animal PET/MRI.

Animal model

**Stereotactic injection of U87 cells**
- human glioblastoma, 50,000 cells/μl
- in the striatum (L: −2.0, AP: −0.5, DV: −3.0 mm) of nude mice

**Tumor monitoring with MR Imaging**

T2 weighted images of a nude mouse brain showing the growth of a U87 tumor A) 7 days post-injection and B) 16 days post-injection in the coronal plane.

In vitro autoradiography

**Total Binding**
(S)-(−)-[18F]Fluspidine 0.92 nM

**Non specific binding**
SA 4503 10 μM

**SA 4503 (nM)**

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<th>1</th>
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**Total fluspidine (nM)**

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<tr>
<th>0</th>
<th>20</th>
<th>40</th>
<th>60</th>
<th>80</th>
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**B\_\text{max} (nM)**
1756.4±43.25

**K\_\text{D} (nM)**
17.5±1.3

**Relative density**
3.6

PET imaging of (S)-(−)-[18F]fluspidine

**in healthy mice and S1R K.O. mouse**

**in mice bearing U87 orthotopic tumor**

**Peak-to-end ratio**

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<thead>
<tr>
<th></th>
<th>mean</th>
<th>SD</th>
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<tbody>
<tr>
<td>tumor</td>
<td>1.65±0.001</td>
<td>0.46</td>
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<tr>
<td>contralateral</td>
<td>2.19</td>
<td>0.59</td>
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<tr>
<td>healthy striatum</td>
<td>0.01</td>
<td>0.001</td>
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**Twosided paired student T test, p<0.05, *compared to CL**

**In vivo validation of the specific binding for S1R shown by the higher SUV values obtained in striatum of healthy mice (n=3) compared to the S1R K.O. mouse (n=1)**

**Time-activity curves of the striatum of healthy mice (n=3), of the tumor region (n=17, average volume: 12 mm³) and the contralateral side(n=17) of tumor mice. The PET image shows spatial uptake inhomogeneities in the tumor**

SUMMARY

- The in vitro autoradiography revealed a higher S1R density in the tumor compared to the contralateral side.
- The PET investigation revealed a significant difference in the pharmacokinetics of (S)-(−)-[18F]fluspidine between tumor and contralateral region, probably related to different S1R availabilities.
- These first results show the suitability of (S)-(−)-[18F]fluspidine for characterization of U87 S1R status.